

DEUTETRABENAZINE FOR THE
TREATMENT OF INVOLUNTARY
MOVEMENTS IN PATIENTS WITH TARDIVE
DYSKINESIA (AIM-TD): A DOUBLE-BLIND
RANDOMIZED, PLACEBO-CONTROLLED,
PHASE 3 TRIAL

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EPIDEMIOLOGY

- Tardive dyskinesia
 - Based on definition of DSMV, diagnosis of tardive dyskinesia can only be confirmed after the symptoms sustain at least one month after discontinuation of medication (i.e. typical and atypical antipsychotics or antiemetic)
- Nonmodifiable risk factors-
 - Post-menopausal women, elderly patients and African Americans more likely to develop tardive dyskinesia.

MODIFIABLE RISK FACTORS

- Around 30% of patients treated with first-generation antipsychotics and 20.7 % in patients who are treated with second-generation antipsychotics are affected with tardive dyskinesia.
- Among first-generation antipsychotic, perphenazine has the higher incidence (34.4%).
- With history of using first-generation antipsychotic, patients treated with atypical antipsychotic could still develop tardive dyskinesia.
- That in 87% of cases are considered irreversible is an unresolved issue, despite discontinuation of offending agents.

MANAGEMENT OF TD

- Lowering the dose of or discontinuing causative agents.
- Switching to low potency agents.
- Valbenazine is currently the only FDA approved drug for TD.

MECHANISM OF ACTION

-
- Vesicular monoamine transporter-2 (VMT-2) is responsible for storage and release of dopamine from synaptic vesicles in the brain
 - Tetrabenazine first approved VMT-2 for chorea associated Huntington's disease, however, high peak concentrations and plasma fluctuations cause tolerability concerns
 - Deutetrabenazine is a highly selective VMT-2 inhibitor that lacks the toxic effects of tetrabenazine also is approved for chorea associated Huntington's disease

■ OBJECTIVES

■ Primary Endpoint

- Change in AIMS severity score from baseline to week 12

■ Secondary Endpoints

- Proportion of patients who had investigator-assessed treatment success at week 12
- Change in the modified Craniocervical Dystonia Questionnaire (mCDQ)-24 from baseline to week 12
- Proportion of patients who had treatment success as measured by the Patient Global Impression of Change (PGIC)

■ Safety

Patient weight, lab test, ECG, Unified Parkinson's Disease, Barnes Akathisia, HADS test for anxiety or depression, Columbia suicide severity rating Scale and Empowrth, montreall cognitive assessment.

Inclusion Criteria	Exclusion Criteria
● 18-80 years old ● Clinical diagnosis of tardive dyskinesia for at least 3 months ● History of use of dopamine receptor antagonists for at least 3 months ● Total AIMS score of 6 or more ● Patient with underlying psychiatric illness had to be stable, with no change in psychoactive medication for at least 30 days before screening, or 45 days for antidepressants	● Received treatment within 30 days of screening with tetrabenazine, reserpine, metirosine, medications with strong anticholinergic properties, dopamine antagonizing antiemetics, stimulants, monoamine oxidase inhibitors, levodopa or dopamine agonists, or botulinum toxin within 3 months ● Patients with a neurological condition other than tardive dyskinesia that could interfere with assessment ● Suicidal ideation within 6 months of screening ● Prolonged QT interval

STUDY DESIGN

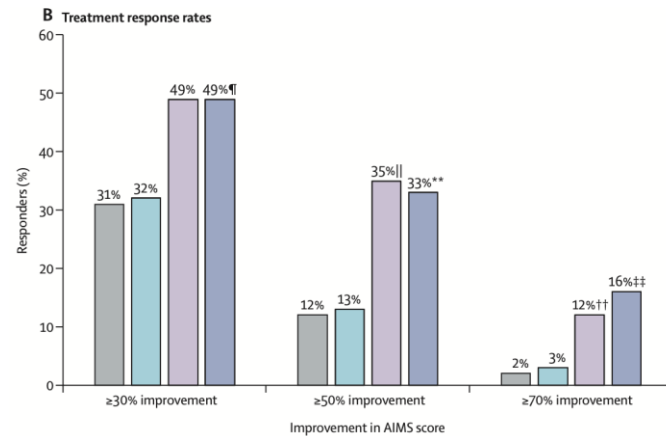
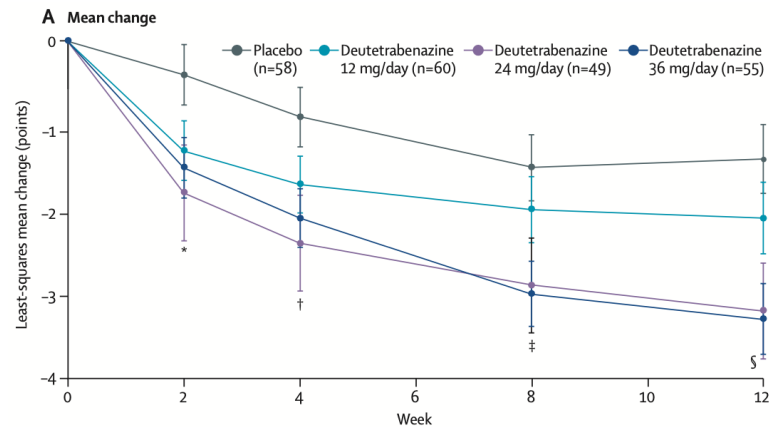
DOUBLE-BLIND,
RANDOMIZED,
PLACEBO-CONTROLLED,
PHASE 3 STUDY

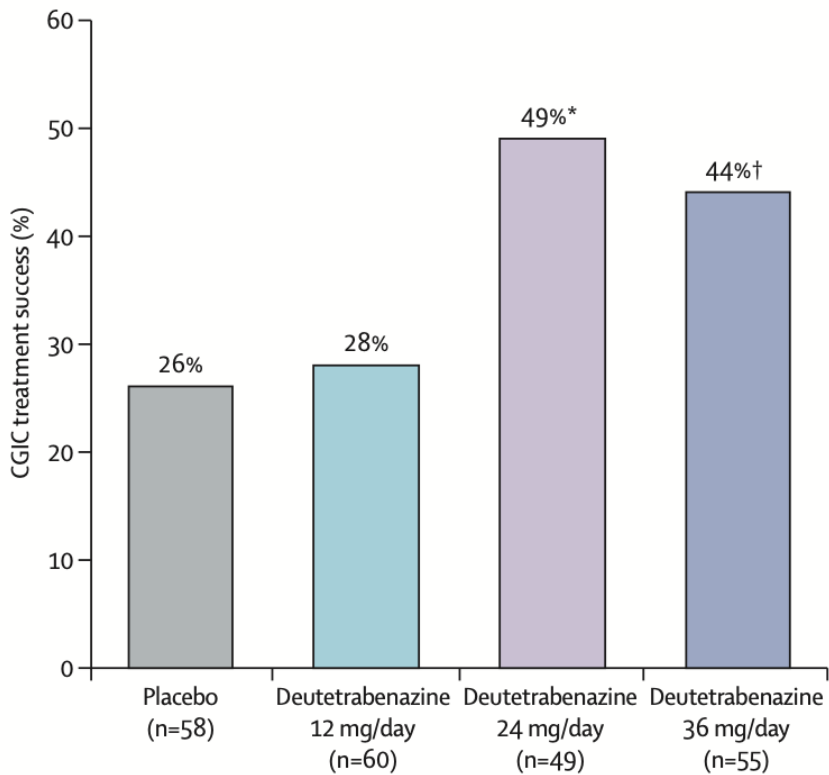
PATIENT DEMOGRAPHICS

- Baseline characteristics were similar between treatment groups and safety population
- Rates of patients receiving dopamine receptor antagonists at baseline were similar between placebo and all treatment groups
- AIMS score at baseline was 9.5 in placebo, 9.6 in deutrabenazine 12 mg/day, 9.4 in deutrabenazine 24 mg/day, and 10.1 in deutrabenazine 36 mg/day

	Placebo group (n=72)	Deutetrabenazine groups			Total (N=293)
		12 mg/day (n=74)	24 mg/day (n=73)	36 mg/day (n=74)	
Demographics					
Age (years)	54.6 (12.1)	57.0 (10.0)	55.6 (11.3)	58.3 (11.6)	56.4 (11.3)
Sex					
Female	37 (51%)	42 (57%)	41 (56%)	42 (57%)	162 (55%)
Male	35 (49%)	32 (43%)	32 (44%)	32 (43%)	131 (45%)
White race	59 (82%)	58 (78%)	54 (74%)	61 (82%)	232 (79%)
Clinical characteristics					
Duration of tardive dyskinesia (years)	6.0 (5.4)	5.5 (5.4)	5.0 (6.0)	5.9 (5.3)	5.6 (5.5)
Use of dopamine receptor antagonists	56 (78%)	56 (76%)	57 (78%)	53 (72%)	222 (76%)
Typical antipsychotics	2 (3%)	7 (10%)	4 (6%)	5 (7%)	18 (6%)
Atypical antipsychotics	51 (71%)	46 (62%)	45 (62%)	40 (54%)	182 (62%)
Both	3 (4%)	3 (4%)	8 (11%)	8 (11%)	22 (8%)
Primary psychiatric illness					
Schizophrenia	31 (43%)	32 (43%)	42 (58%)	40 (54%)	145 (50%)
Schizoaffective disorder	11 (15%)	8 (11%)	7 (10%)	4 (5%)	30 (10%)
Bipolar	17 (24%)	15 (20%)	7 (10%)	12 (16%)	51 (17%)
Depression	11 (15%)	17 (23%)	11 (15%)	16 (22%)	55 (19%)
Other	2 (3%)	2 (3%)	6 (8%)	2 (3%)	12 (4%)
Data are mean (SD) or n (%).					
Table 1: Baseline characteristics (safety population)					

RESULTS





RESULTS

	Placebo group (n=72)	Deutetrabenazine groups			All patients (N=293)	
		12 mg/day (n=74)	24 mg/day (n=73)	36 mg/day (n=74)	All doses (n=221)	
Patients with at least one AE						
AE	34 (47%)	36 (49%)	32 (44%)	38 (51%)	106 (48%)	140 (48%)
Serious AE	4 (6%)	2 (3%)	6 (8%)	4 (5%)	12 (5%)	16 (6%)
Treatment-related AE	19 (26%)	13 (18%)	11 (15%)	18 (24%)	42 (19%)	61 (21%)
AE leading to dose reduction	0	0	1 (1%)	3 (4%)	4 (2%)	4 (1%)
AE leading to dose suspension	2 (3%)	3 (4%)	1 (1%)	1 (1%)	5 (2%)	7 (2%)
AE leading to discontinuation	2 (3%)	4 (5%)	2 (3%)	3 (4%)	9 (4%)	11 (4%)
Deaths	0	0	1 (1%)	1 (1%)	2 (1%)	2 (1%)
AEs of interest						
Nervous system disorders	10 (14%)	6 (8%)	6 (8%)	16 (22%)	28 (13%)	38 (13%)
Akathisia	0	0	1 (1%)	0	1 (<1%)	1 (<1%)
Dyskinesia	0	0	1 (1%)	1 (1%)	2 (1%)	2 (1%)
Headache	4 (6%)	5 (7%)	2 (3%)	5 (7%)	12 (5%)	16 (5%)
Migraine	0	0	0	1 (1%)	1 (<1%)	1 (<1%)
Parkinsonism	0	0	0	1 (1%)	1 (<1%)	1 (<1%)
Sedation	0	0	0	1 (1%)	1 (<1%)	1 (<1%)
Somnolence	3 (4%)	0	1 (1%)	3 (4%)	4 (2%)	7 (2%)
Psychiatric disorders	7 (10%)	10 (14%)	7 (10%)	9 (12%)	26 (12%)	33 (11%)
Anxiety	2 (3%)	3 (4%)	2 (3%)	3 (4%)	8 (4%)	10 (3%)
Anxiety disorder	0	1 (1%)	0	0	1 (<1%)	1 (<1%)
Depressed mood	0	1 (1%)	0	0	1 (<1%)	1 (<1%)
Depression	0	1 (1%)	3 (4%)	1 (1%)	5 (2%)	5 (2%)
Irritability	0	1 (1%)	0	1 (1%)	2 (1%)	2 (1%)
Suicidal ideation	0	0	2 (3%)	1 (1%)	3 (1%)	3 (1%)
Other AEs						
Diarrhoea	2 (3%)	1 (1%)	3 (4%)	5 (7%)	9 (4%)	11 (4%)
Nausea	7 (10%)	1 (1%)	1 (1%)	1 (1%)	3 (1%)	10 (3%)
Nasopharyngitis	1 (1%)	4 (5%)	3 (4%)	2 (3%)	9 (4%)	10 (3%)
Fatigue	1 (1%)	1 (1%)	2 (3%)	3 (4%)	6 (3%)	7 (2%)
Dry mouth	0	3 (4%)	0	2 (3%)	5 (2%)	5 (2%)
Muscle spasms	0	0	0	3 (4%)	3 (1%)	3 (1%)
Hypertension	1 (1%)	0	0	3 (4%)	3 (1%)	4 (1%)

AE=adverse event.

Table 3: Adverse events (safety population)

	Placebo group (n=58)	Deutetrabenazine groups		
		12 mg/day (n=60)	24 mg/day (n=49)	36 mg/day (n=55)
PGIC				
Treatment success (%; 95% CI)	18 (31%, 20.6 to 43.8)	14 (23%, 14.4 to 35.4)	22 (45%, 31.9 to 58.7)	22 (40%, 28.1 to 53.2)
Odds ratio (95% CI) vs placebo	..	0.69 (0.30 to 1.56); p=0.372	1.82 (0.83 to 3.99); p=0.134	1.51 (0.69 to 3.29); p=0.296
mCDQ-24				
Least-squares mean change (SE)	-7.1 (2.1)	-5.9 (2.1)	-10.6 (2.2)	-11.6 (2.1)
Least-squares mean difference (SE, 95% CI) vs placebo	..	1.2 (2.79, -4.26 to 6.74; p=0.656)	-3.5 (2.94, -9.25 to 2.35; p=0.242)	-4.4 (2.87, -10.10 to 1.21; p=0.123)
mCDQ-24 subdomains (least-squares mean change [SE]; p value vs placebo)				
Activities of daily living	-6.8 (2.3)	-7.0 (2.3); p=0.939	-8.2 (2.5); p=0.659	-11.8 (2.3); p=0.111
Emotional	-7.3 (2.3)	-0.5 (2.4); p=0.033	-6.7 (2.5); p=0.865	-5.9 (2.3); p=0.664
Pain	-6.1 (2.9)	-4.9 (3.0); p=0.764	-15.2 (3.2); p=0.029	-15.5 (2.9); p=0.020
Social	-3.6 (2.5)	-2.3 (2.6); p=0.709	-4.8 (2.7); p=0.745	-10.5 (2.5); p=0.053
Stigma	-9.9 (2.9)	-11.9 (2.9); p=0.598	-17.8 (3.1); p=0.055	-13.3 (2.9); p=0.388

PGIC=Patient Global Impression of Change. mCDQ-24=modified Craniocervical Dystonia Questionnaire-24.

Table 2: Patient-reported outcomes (modified intention-to-treat population)

RESULTS

Strengths

- Multicenter, double-blind, randomized, placebo-controlled
- Patient characteristics were similar in all groups
- Appropriate statistical measurements used
- Used blinded central video raters who were movement disorder experts

Limitations

- Placebo group had a notable response
- Use of PGIC and mCDQ-24 (patient-reported outcomes measures)
- Study was funded by Teva Pharmaceutical Industries

DISCUSSION

DISCUSSION

- Comparing with other studies
 - ARM-TD trial, deutetrabenazine significantly reduced AIMS scores from baseline to week 12 vs placebo. Treatment success on CGIC also favored deutetrabenazine. Deutetrabenazine and placebo groups showed low rates of psychiatric adverse events.
 - In the open-label trial on 2018, significant change in mean AIMS score in week 108 indicated that long-term treatment with deutetrabenazine was efficacious, safe, and well tolerated in patients with TD.
 - In the OLE trial, severe tardive dyskinesia patients with baseline total AIMS score >14 had clinically meaningful reductions in AIMS score.

CONCLUSION

Deutetrabenazine 24 mg/day or 36 mg/day was shown to be effective treatment for tardive dyskinesia and well tolerated

Patients' doses can be individualized based on their response and side effects

Further monitoring and studies need be completed, but deutetrabenazine may be an effective additive treatment for patients experiencing tardive dyskinesia

PRACTICAL IN OUR PRACTICE

- The studies prove the significance improvement in AIMS score for the efficacy in deubentazine.
- Cost is much cheaper than valbenazine.
- Even though our patients meet the inclusion criteria and consider all the advantages, the prevalence of TD is low, so it is recommended not to start deutetrabenazine as first line treatment.

REFERENCE

1. Anderson KE, Stamler D, Davis MD, et al. Deutetrabenazine for treatment of involuntary movements in patients with tardive dyskinesia (AIM-TD): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Psychiatry*. 2017;4(8):595-604. doi:10.1016/S2215-0366(17)30236-5
2. D'Abreu A., Akbar U. and Friedman JH. Tardive dyskinesia: Epidemiology. *J. Neurol. Sci.* 2018; 389, 17-20. <https://www.clinicalkey.com.proxy.lib.ohio-state.edu/#!/content/journal/I-s2.0-S0022510X18300650?scrollTo=%23hl0000142>. Accessed December 23, 2021.
3. Solmi M, Pigato G, Kane JM, Correll CU. Clinical risk factors for the development of tardive dyskinesia. *Journal of the Neurological Sciences*. 2018;389:21-27. doi:10.1016/j.jns.2018.02.012
4. Fernandez HH, Factor SA, Hauser RA, et al. Randomized controlled trial of deutetrabenazine for tardive dyskinesia. *Neurology*. 2017;88(21):2003-2010. doi:10.1212/wnl.0000000000003960. Accessed December 20th, 2021.
5. Fernandez HH, Stamler D, Davis MD, et al. Long-term safety and efficacy of deutetrabenazine for the treatment of tardive dyskinesia. *J Neurol Neurosurg Psychiatry*. 2019 Dec;90(12):1317-1323. doi: 10.1136/jnnp-2018-319918. Accessed December 19th, 2021.
6. Chajjale N, Bona J, Barkay H, et al. Deutetrabenazine Reduces Severe Tardive Dyskinesia Movements in a 3-year Open-Label Extension Trial. *CNS Spectr*. 2021 Apr;26(2):156. doi: 10.1017/S1092852920002497. PMID: 34127115.

Presentation Evaluation Form

For Preceptor

Student's Name: Esther Tzai	Topic: Deutetrabenazine for the treatment of involuntary movements in patients with Tardive Dyskinesia
Preceptor's Name: Deepak Patel	Site: Ohio Hospital For Psychiatry
Preceptor's Signature:	Date: 12/28/21

	Criteria				Points
	4	3	2	1	
Body Language	Movements seemed fluid and helped the audience visualize.	Made movements or gestures that enhanced articulation.	Very little movement or descriptive gestures.	No movement or descriptive gestures.	4
Eye Contact	Holds attention of entire audience with the use of direct eye contact.	Consistent use of direct eye contact with audience.	Displayed minimal eye contact with audience.	No eye contact with audience	3
Introduction and Closure	Student delivers opening and closing remarks that capture the attention of the audience and set the mood.	Student displays clear introductory or closing remarks.	Student clearly uses either an introductory or closing remark, but not both.	Student does not display clear introductory or closing remarks.	3
Pacing	Good use of drama and student meets apportioned time interval.	Delivery is patterned, but does not meet apportioned time interval.	Delivery is in bursts and does not meet apportioned time interval.	Delivery is either too quick or too slow to meet apportioned time interval.	3
Poise	Student displays relaxed, self-confident nature about self with no mistakes.	Makes minor mistakes, but quickly recovers from them; displays little or no tension.	Displays mild tension; has trouble recovering from mistakes.	Tension and nervousness is obvious; has trouble recovering from mistakes.	3
Voice	Consistent use of fluid speech, complete sentences, correct English and no "fillers" (um, uh, and stuff).	A few instances of use of non-fluid speech, incomplete sentences, incorrect English, or fillers.	Significant issues with one of the defined elements (fluid speech, complete sentences, correct English and no "fillers").	Consistent issues with two or more of the defined elements (fluid speech, complete sentences, correct English and no "fillers").	3
Content	Content is at the appropriate level of knowledge of the audience, appropriate selection and definition of terminology	Most of the content is appropriate to the knowledge level of the audience	At least some of the content is appropriate to the knowledge level of the audience	Consistently speaks above or below the knowledge level of the audience	3

Handouts	Handout was in (1)logical order, (2) contained appropriate content, and (3) useful for future reference	Refer to box for score of 4 – Handout met two of the three requirements	Refer to box for score of 4 – Handout met one of the three requirements	Refer to box for score of 4 – Handout did not meet any of the three requirements.	4
The student must earn at least a 23/32 to consider this a satisfactory assignment for their portfolio.				TOTAL:	26 /32

Preceptor Comments (including 2 strengths and 2 areas for improvement):